TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LTS 2004/001 PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/EP2005/002185	International filing date *(day/month/year)* 02.03.2005	Priority date *(day/month/year)* 09.03.2004
International Patent Classification (IPC) or national classification and IPC A61K47/48		
Applicant LTS LOHMANN THERAPIE-SYSTEME AG		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/002185

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed

☐ the translation of the international application into _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3(a) and 23.1(b))

☐ publication of the international application (Rule 12.4(a))

☐ international preliminary examination (Rule 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-17 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 1-15 received by this Authority on 11.11.2006 with letter of 10.11.2002

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets 1/2, 2/2 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/002185

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims, Nos. 1-6 and 8-15 in part

because:

☐ the said international application, or said claims Nos. _____
relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 1-6 and 8-15 in part

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-15	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-15	NO
Industrial applicability (IA)	Claims	1-15	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

1 Reference is made to the following documents:

D1: WO 02/089776 A (LTS LOHMANN THERAPIE-SYSTEME AG; KREUTER, JOERG; LANGER, KLAUS; WEBER,) 14 November 2002 (2002-11-14)

D2: ARTEMOV DMITRI et al: "MR molecular imaging of the Her-2/neu receptor in breast cancer cells using targeted iron oxide nanoparticles" Magnetic Resonance In Medicine, Academic Press, Duluth, MN, US, Vol. 49, No. 3, March 2003 (2003-03), pages 403-408, XP002348193 ISSN: 0740-3194

D3: WU, XINGYONG et al: "Immunofluorescent labeling of cancer marker Her2 and other cellular targets with semiconductor quantum dots" Nature Biotechnology, Vol. 21, No. 1, 2003, pages 41-46, XP002393171

D4: HARMA, HARRI et al: "Zeptomole detection sensitivity of prostate-specific antigen in a rapid microtitre plate assay using time-resolved fluorescence" Luminescence, Vol. 15, No. 6, 2000, pages 351-355, XP002393172

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Document **D1** was mentioned in the application as EP 1 392 255 and discloses the production of exactly the same particles based on serum albumin as in the present application. Since, however, the claims require the presence of an antibody, the present claims differ from **D1** precisely by that presence of the antibody. That difference is also indicated in the present application as being a solution to the problem of concentrating nanoparticles in specific cells.

Although document **D2** discloses different nanoparticles, they are also bound to a biotinylated anti-HER2 antibody following thiolation via neutravidin. As in the present application, the nanoparticles are thus targeted to HER2-positive cells.

Document **D3** discloses different nanoparticles, which are also bound to a biotinylated anti-HER2 antibody via avidin. As in the present application, the nanoparticles are thus targeted to HER2-positive cells.

Document **D4** discloses different nanoparticles, which are also bound to a biotinylated antibody via avidin. The nanoparticles in that document are not, however, targeted to receptor-positive cells.

Either document **D2** or document **D3** is considered the closest prior art, since those documents solve

the same problem (targeted control of nanoparticles for enrichment in specific cells). The nanoparticles claimed in the present application differ from that prior art in that the nanoparticles are protein-based.

The examples show that the protein-based nanoparticles also solve the problem of providing targeted nanoparticles. The examples also show that the claimed nanoparticles actually solve the problem.

In view of the teaching in **D2**, however, a person skilled in the art already knows that the targeting of the nanoparticles can be put down to the presence of the antibody. The use of protein-based nanoparticles as per **D1** cannot in this context make any contribution to inventive step. Although the avidinylated nanoparticles differ from the nanoparticles described in **D2**, the applicant has not demonstrated any technical effect that can be attributed to that difference.

The claims of the present application thus fail to meet the requirements of PCT Article 33(3) in respect of inventive step.

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/*month/year*)	Filing date (day/*month/year*)	Priority date (valid claim) (*day*/month/*year*)
EP 1 598 419	23.11.2005	27.02.2004	28.02.2003
WO 2004/076658	10.09.2004	27.02.2004	28.02.2003

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/*month/year*)	Date of written disclosure referring to non-written disclosure (*day*/month/*year*)

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1 does not meet the requirements of PCT Article 6, since the subject matter for which protection is sought is not clearly defined. The claim attempts to define the subject matter by the result to be achieved; thus only the problem to be solved is defined, without the technical features needed to achieve that result being specified.

Claims 1-6 and 8-15 relate to an extremely large number of possible support systems, and to methods for the production thereof. Support and disclosure in the sense of PCT Articles 6 and 5, however, can be found for only a very small number of the claimed support systems. In the examples, only one specific nanoparticle (made of gelatine) is produced and is administered in a controlled manner using two different antibody conjugates. It is therefore not clear whether the requirements of PCT Article 5 are actually satisfied within the claimed range.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: Box III.

Claims 1-6 and 8-15 relate to an extremely large number of possible support systems, and to methods for the production thereof. Support and disclosure in the sense of PCT Articles 6 and 5, however, can be found for only a very small number of the claimed support systems. In the examples, only one specific nanoparticle (made of gelatine) is produced and is administered in a controlled manner using two different antibody conjugates. The application fails to meet the requisite requirements to such an extent that the non-compliance was taken into account when determining the scope of the search (PCT Guidelines 9.19 and 9.23).

The search in respect of claims 1-6 and 8-15 was restricted to those claimed support systems which are supported by examples in the description. The examination was therefore restricted accordingly.